Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

February 17, 2006

Public Information and Records Integrity Branch (PIRIB)
Office of Pesticide Programs (OPP)
Environmental Protection Agency
Room 119, Crystal Mall #2, 1801 S. Bell Street
Arlington, VA

Attention: Docket ID Number EPA-HQ-OPP-2005-0252

Dear Sir/Madam:

The Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency (Cal/EPA) has reviewed the human heath risk assessment by the U.S. Environmental Protection Agency (USEPA) for the chemical, iodomethane (Public Docket EPA-HQ-OPP-2005-0252). This chemical is under consideration by the Agency for the use as a pesticide in soil fumigation. It has been identified as a potential partial replacement for methyl bromide.

We are also evaluating the potential use of iodomethane as a fumigant in California. Since the DPR risk assessment is on-going, our comments at this time are limited to three areas: 1) selection of the no-observed-adverse-effect level [NOAEL] for the rabbit developmental toxicity study, 2) oncogenic potential of iodomethane, and 3) developmental neurotoxicity potential of iodomethane.

We are concerned about the NOAEL that USEPA selected for the fetal death in the pregnant rabbits exposed to iodomethane by inhalation exposure (6 hours per day) during gestation. In this rabbit developmental toxicity study, there were increased incidences of late resorption (dead fetuses resorbed within the uterus), and fetuses born dead. USEPA established a NOAEL of 10 ppm based on "fetal loss and decreased fetal weights (↓20%)." This NOAEL dose of 10 ppm was input to the physiologically-based pharmacokinetic (PBPK) model, which resulted in two human equivalent concentrations (HECs) of 4 ppm and 17 ppm, for 24 hours. The 4 ppm was subsequently chosen as one of the HECs to evaluate acute human exposure. We feel that the USEPA should consider the use of 2 ppm, a value determined by the scientist who conducted the study as the NOAEL, to develop the HECs. It was unclear to us how USEPA established the NOAEL at 10 ppm since neither data nor discussion of the dose-response relationship was presented in the risk assessment. Our review of the data found that at 2 ppm, the incidence

for late resorption was 3.1% of fetuses per litter, 2-fold higher than the control group (1.7%). At 10 ppm, the incidence (11%) was about 7-fold that of controls. While this increase was not statistically significant, it was clearly treatment-related and along a steady-rise of the dose-response curve. The determination of the NOAEL at 10 ppm should consider the much higher incidence (22%, statistical significance at $p<0.01$) at 20 ppm, just two-fold increase in the dose. Fetal toxicity, through the proposed mode of action, is a pertinent concern for human exposure to iodomethane, especially women of child-bearing age.

Thus, the use of the NOAEL of 2 ppm to evaluate human exposure would result in a difference of 5-fold, considering the NOAEL alone, between DPR and USEPA. There could be additional differences in the calculation of the reference concentration due to other factors (not applying PBPK model and RfC methodology). These differences may result in a total of a several-fold lower reference concentration for this endpoint, a significant impact on the conclusion regarding whether human exposure would be of concern. We recommend that the USEPA give additional consideration for the biological significance of fetal death from iodide at 10 ppm, to ensure adequate protection during developmental stages for humans.

With regards to the oncogenicity assessment, we think the consideration should not be focused only on the species sensitivity of thyroid tumors, and that a more thorough discussion on the overall weight of evidence is warranted. In terms of the species sensitivity for thyroid tumors, USEPA classified iodomethane as "not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis." The qualifier on the classification was based on "*evidence that rats are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance*." This was referenced to the USEPA Cancer Risk Assessment Guidelines, but no support for this classification was given, either as a general rule or for iodomethane specifically. In terms of the weight of evidence consideration for carcinogen classification, we are concerned that the Agency did not provide adequate support from the overall iodomethane database. There is suggestive evidence for oncogenicity involving more than only the thyroid. Iodomethane is a mutagen and has been shown to induce tumors at the site of contact (skin) and other effects at remote sites (lung tumor by intraperitoneal injection; salivary gland metaplasia, and cervical and uterine fibroma by inhalation exposure) in laboratory animals. We recommend that a clear rationale for the oncogenic potential be presented and supported by pertinent literature citation and the data for iodomethane.

In the USEPA risk assessment, the potential developmental neurotoxicity was not addressed. The rationale given was that iodomethane was a non-food use chemical and therefore, precluded from

considerations of provisions under the Food Quality Protection Act. We are very concerned about this potential in human exposure, given that normal thyroid function is crucial for neurodevelopment. While residues may not be present in crops grown on treated soil, workers and bystanders as well as residents living near the treated fields will be exposed to it in the air. In addition, iodomethane has been shown to cause neurotoxicity in laboratory animals and humans. The question remains as to what neurodevelopmental harm could result in the neonate, if the established NOAEL for risk assessment ensures only fetal survival. We urge the USEPA to give serious considerations to this concern.

Thank you for the opportunity to provide comment on this public document. If you have any questions, please feel free to contact Joyce Gee at jgee@cdpr.ca.gov, or Gary Patterson at gpatterson@cdpr.ca.gov or (916) 445-4233.

Sincerely,

[original signed by]

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